Antibiotics: the New Bard-Parker for Appendicitis?

History:
In 1735, Dr. Claudius Amyand performed the world’s first successful appendectomy at St. George’s Hospital in London. The patient was an 11-year-old boy whose appendix had become perforated by a pin he had swallowed.

Appendicitis firmly remained a surgical disease for more than 270 years. In 2012 the British Medical Journal irreverently asked, “Should conservative treatment of appendicitis be first line therapy?”

Role of Conservative treatment?
Even as early as 2009 (Br J Surg. 2009 July; 96 (7) 830), British surgeons randomized 202 consecutive adults with appendicitis to antibiotics (IV x 24 hours plus oral antibiotics x 10 days) or standard appendectomy. Recurrent appendicitis occurred in 15 patients (13.9%) after a median of one year. A third of the recurrences appeared within 10 days. Major complications were threefold higher in patients who had had an initial appendectomy.

Since 2012, several studies have confirmed the BMJ’s 2012 premise. Non-surgical management of acute uncomplicated appendicitis is a viable, safe and cost-effective tool.
**The Finns and APPAC:**
In 2015, Finnish surgeons (JAMA. June 16, 2015, APPAC study) randomized 530 adults with CT confirmed, uncomplicated appendicitis to antibiotics (intravenous ertapenem (1 g/d) for three days followed by seven days of oral levofloxacin (500 mg once daily) or appendectomy. Seventy patients (27.3%) underwent appendectomy within one year of initial presentation for appendicitis. Those 70 who underwent appendectomy did not experience significant complications.

In a five year follow-up of the APPAC study (JAMA. 2018; 320(12) 1259-1265), among patients who were initially treated with antibiotics, the likelihood of late occurrence within five years was 39.1%. At five years, the overall complication rate (surgical site infections, incisional hernias, abdominal pain and obstructive symptoms) was 24.4% (n=60/246) in the appendectomy group and 6.5% in the antibiotic group.

**Or do you even need antibiotics?**
And then British surgeons (British Journal of Surgery. September 19, 2017) decided to really test the water. Observing that uncomplicated appendicitis may resolve spontaneously, the authors randomized 245 patients with uncomplicated appendicitis to management with a no antibiotic regimen (IV fluids, antipyretics and analgesics) or a four day course of antibiotics with supportive care and followed them for a median of 19 months. **There was no difference in total treatment failure rate between the groups:** 29 of 124 (23.4%) in the no-antibiotic group and 25 of 121 (20.7%) in the antibiotic group.

**How about kids?**
- Huang et al. (JAMA Pediatrics. 2017; 171 (5): 426–434.) identified 404 unique patients with uncomplicated appendicitis (aged 5-15 years) enrolled in randomized controlled studies. Non-operative treatment was successful in 152 of 168 patients (90.5%). Subgroup analysis showed that the risk for treatment failure in patients with appendicolith increased.
- In a foretaste of shared decision making, Tanaka et al. (J Pediatr Surg. 2015 Nov; 50(11):1893-7) asked parents of kids with uncomplicated appendicitis to select either operative (laparoscopic surgery) or non-operative treatment on admission. For non-operative treatment, intravenous injection of antibiotics was continued until serum C-reactive protein concentration decreased to below 0.5mg/dL. Eighty-six patients chose operative treatment, and 78 chose non-operative treatment. There were no differences in the length of hospital stays between the two groups. Ileus occurred in two operatively treated patients, while recurrence of appendicitis occurred in 22 non-operatively treated patients (28.6 %) after an average of 4.3years of follow-up.

Steiner et al. (Eur J Pediatr. 2017; 176(4): 521) studied 197 children with uncomplicated appendicitis who were treated with IV antibiotics for 3 to 5 days. The success rate for conservative treatment was 87% (at 18 months), with shorter hospital stays compared to children who eventually needed surgery. Intraluminal fluid on sonography was the only prognostic sign for failed treatment (odds ratio = 10.2). Patients who failed conservative treatment were successfully operated without significant morbidity.

**“Up to Date”**
UTD suggests the following criteria for non-surgical treatment of appendicitis in children:
- Abdominal pain for <48 hours
- White blood cell count ≤18,000/microL
- Normal C-reactive protein
- **No** appendicolith present on imaging
- Appendix diameter ≤1.1 cm on imaging
- No preoperative concern for rupture based upon clinical findings
Antibiotics may be especially appropriate in children who meet the above criteria and who have comorbidities that raise the risk of appendectomy. Antibiotic protocols vary widely, but typically include 1 to 2 days of inpatient broad spectrum intravenous therapy (eg, piperacillin-tazobactam, ceftiraxone, metronidazole and ciprofloxacin) until resolution of symptoms and normalization of white blood cell count occur followed by oral antibiotics (eg, amoxicillin-clavulanic acid or ciprofloxacin and metronidazole) as an outpatient.

My Take:
- Non-surgical management of acute uncomplicated appendicitis is a viable, safe, cost-effective alternative to appendectomy in both adults and children.
- CT scanning/sonography is important to identify complications of appendicitis and appendicoliths (and Steiner would say luminal fluid) that are contra-indications to non-surgical management.
- What a great clinical scenario to consider Shared Decision Making!

Restasis:
Dry Eyes, an Indian Tribe, Filter Paper and Pharma Greed

Lisa Schwartz and Steven Woloshin in a JAMA Internal Medicine, February 2018 Viewpoint expose Allergan Pharmaceutical’s duplicitous maneuvering for their blockbuster drug Restasis. Restasis (cyclosporine ophthalmic emulsion) brought in $8.8 billion in US sales between 2009 and 2015, including $2.9 billion through Medicare part D.

FDA Approval:
In 1999, the FDA unanimously turned down Allergan’s request for approval of Restasis based on two identical studies that showed minimal and inconsistent findings of efficacy. Allergan then dredged the same data four more times. In 2003, the FDA approved Restasis based on a surrogate sign, the Schirmer response (10 mm of moisture on a filter paper strip 5 minutes after placed in the eye). Results: 15% of the Restasis patients got 10mm on the filter paper compared with 5% of the placebo patients. The FDA approval occurred in spite of the clinical trials that showed that Restasis did not improve symptom scores compared to placebo.

Other Countries:
Australia’s Therapeutic Goods Administration, their drug regulatory board, found “Minimal or no benefit over and above placebo.” Restasis is not approved in Australia, the European Union or New Zealand. In 2010 Canada approved Restasis, but it is not covered by their health insurance plans.

Up to Date
“Topical cyclosporine has been found to be relatively safe and well tolerated; although it is not clear that it leads to a clinically important benefit in the treatment of dry eyes.” (Sacchetti et al. British Journal of Ophthalmology. 2014, 98 (8): 1016–22.)

Why has Restasis succeeded in the US?
- Allergan has extensively marketed – mongered – dry eyes and Restasis. They spent $645 million on direct-to-consumer advertising. Their advertising includes a patient “dry eye” quiz that the patient is encouraged to take and print out for their physician.
- Allergan aggressively markets to clinicians whose source of drug information is often limited to pharmaceutical company spin on its own myopic data. Schwartz and Woloshin point out that payers, clinicians and consumers often do not have access to independent drug information.
Native American Tribe
In a companion Viewpoint in JAMA Internal Medicine, February 2018, attorneys Ablavsky and Larrimore describe Allergan’s strategy to sell their patents to the St. Regis Mohawk tribe (upstate New York) to delay the market entry of generic competitors. This Native American tribe will exclusively license the patents back to Allergan. The deal allows the tribe, the patents’ legal owner, to assert what is known as legal sovereign immunity—a bizarre principle to my mind. Sovereigns cannot be sued without their consent. Mylan Pharmaceuticals, a generic manufacturer is challenging the patents. Stay tuned.

My Take:
- It is demoralizing (yes, I am tearful) that none of the Restasis trials ever showed symptom relief superior to placebo.
- The FDA should take a lead from other countries to recognize that surrogate endpoints, e.g. filter paper in your eye, have limited clinical usefulness.
- Good RX reports you can buy this boondoggle for $529 per month.

Dear colleagues,
Are you seeing more clearly now?
Happy New Year!